New propellent gases and their use in pharmaceutical preparations

The invention relates to new propellent gases which contain as a typical ingredient 1,1,1,2,3,3,3-heptafluoropropane (TG 227), the use of these propellent gases in pharmaceutical preparations suitable for producing aerosols, and these pharmaceutical preparations themselves.

Aerosols of powdered (micronised) drugs are used widely in therapy, e.g. in the treatment of obstructive diseases of the respiratory tract. If such aerosols are not produced by atomising the pharmaceutical powder or by spraying solutions, suspensions of the drugs in liquefied propellent gases are used. The latter consist primarily of mixtures of TG 11 (trichlorofluoromethane), TG 12 (dichlorodifluoromethane) and TG 114 (1,2-dichloro-1,1,2,2-tetrafluoroethane), optionally with the addition of lower alkanes such as butane or pentane, or with the addition of DME (dimethylether). Mixtures of this kind are known for example from German Patent 1178975.

Owing to their harmful effect on the earth's atmosphere (destruction of the ozone layer, Greenhouse effect) the use of chlorofluorocarbons has become a problem, with the result that the search is on for other propellent gases or propellent gas mixtures which do not have the above-mentioned harmful effects or, at least, have them to a lesser degree.

However, this search has come up against major problems, since propellent gases for therapeutic use have to satisfy numerous criteria which cannot easily be reconciled, e.g. in terms of toxicity, stability, vapour pressure, density and solubility characteristics.

As has now been found, TG 227 (1,1,1,2,3,3,3-heptafluoropropane, optionally in admixture with one of more propellent gases from the group comprising TG 11 (trichlorofluoromethane), TG 12 (dichlorodifluoro-methane), TG 114 (1,2-dichloro-1,1,2,2-tetrafluoroethane), propane, butane, pentane and DME

(dimethylether) is particularly suitable for use in therapeutic preparations.

The compounds to be used in addition to TG 227 are added if the properties of the propellent gas are to be modified, e.g. if the liquefied propellent gas is to have a different density, different pressure or different solubility characteristics. Pharmaceutical preparations based on the propellent gas contain an active substance in finely divided form, usually as a suspension, and generally also contain surface-active substances, e.g. a phospholipid (such as lecithin), an ester of a polyalcohol (such as sorbitol) with higher saturated or unsaturated fatty acids (e.g. stearic, palmitic or oleic acid), such as sorbitan trioleate, or a polyethoxysorbitan ester of a higher, preferably unsaturated fatty acid. The adjuvant may be present in the mixture in dissolved or undissolved form. In some cases, the suspensions produced with the new propellent gas have a tendency to separate out. However, it has been found that the separated suspensions can easily be uniformly distributed again in the suspension medium simply by shaking.

The ratios of quantities of the individual ingredients of the propellent gas mixture may be varied within wide limits. The proportion (in percent by weight) is 10 to 100% in the case of TG 227. The mixture may also contain up to 50% propane and/or butane and/or pentane and/or DME and/or TG 11 and/or TG 12 and/or TG 114. Within the limits specified the ingredients are chosen to add up to 100%. Propellent gas mixtures which contain 30 to 100% TG 227 are preferred.

The proportion of suspended drug in the finished preparation is between 0.001 and 5%, preferably between 0.005 and 3%, more particularly between 0.01 and 2%. The surface-active substances are added in amounts of from 0.01 to 10%, preferably 0.05 to 5%, more

particularly 0.1 to 3% (here, as in the case of the pharmaceutical substances, the percentage by weight of the finished preparation is given). The pharmaceutical substances used in the new preparations may be any of the substances suitable for use by inhalation or possibly for intranasal administration. They include, therefore, in particular betamimetics, anticholinergics, steroids, antiallergics, PAF-antagonists and combinations of these active substances.

The following are given as specific examples:

Examples of betamimetics:
Bambuterol
Bitolterol
Carbuterol
Clenbuterol
Fenoterol
Hexoprenalin
Ibuterol
Pirbuterol
Procaterol
Reproterol
Salbutamol
Salmeterol
Sulfonterol
Terbutalin
Tulobuterol
1-(2-fluoro-4-hydroxyphenyl)-2-[4-(1-benzimidazolyl)-2-methyl-2-butylamino]ethanol

erythro-5'-hydroxy-8'-(1-hydroxy-2-isopropylaminobutyl)-2H-1,4-benzoxazin-3-(4H)-one

1-(4-amino-3-chloro-5-trifluoromethylphenyl)-2-tert.-butylamino)ethanol

1-(4-ethoxycarbonylamino-3-cyano-5-fluorophenyl)-2-

(tert.-butylamino)ethanol.

Examples of anticholinergics:
Ipratropium bromide
Oxitropium bromide
Trospium chloride
Benzilic acid-N-β-fluoroethylnortropine ester methobromide

Examples of steroids:
Budesonide
Beclomethasone (or the 17, 21-dipropionate thereof)
Dexamethason-21-isonicotinate
Flunisolide

Examples of antiallergics:
Disodium cromoglycate
Nedocromil

Examples of PAF-antagonists:
WEB 2086
WEB 2170
WEB 2347

The active substances may also be combined, e.g. betamimetics plus anticholinergics or betamimetics plus antiallergics.

Examples of preparations according to the invention (amounts given in percent by weight):

1)	0.10% Oxitropium bromide	2)	0.3% Fenoterol
	0.01% Soya lecithin		0.1% Soya lecithin
	4.0% Pentane		10.0% Pentane
	95.89% TG 227		70.0% TG 227
			19.6% TG 134a

3) 0.1% Ipratropium bromide
0.1% Soya lecithin
20.0% Pentane
20.0% Butane
49.8% TG 11

4) 0.3% Fenoterol
0.1% Soya lecithin
30.0% TG 11
69.6% TG 227

5) 1.5% Disodium cromoglicate
0.1% Tween 20
98.4% TG 227
1.4% Butane

6) 0.3% Salbutamol
0.2% Span 85
20.0% Pentane
60.0% TG 227
19.5% TG 12

7) 0.15% Fenoterol
0.06% Ipratropium-bromide
0.10% Soya lecithin
40.00% TG 11
19.69% Propane
40.00% TG 227

8) 0.1% Ipratropium-bromide
0.1% Soya lecithin
15.3% Propane
30.5% TG 11
54.0% TG 227